The reorganization of inhibitory synaptic input onto the specific network of neurons encoding the fear memory is a novel, selective, and direct mechanism for limiting conditioned fear responses after extinction. Although the cellular mechanisms underlying these synaptic changes are not yet understood, a large number of studies suggest that NMDA receptors may be involved (Falls et al., 1992; Zimmerman and Maren, 2010). How NMDA receptors mediate both long-term potentiation of excitatory synapses onto BA neurons encoding fear conditioning and the remodeling of perisomatic inhibition onto these neurons after extinction is a fascinating question. Whatever the mechanism, these data are consistent with the idea that extinction involves new learning that suppresses learned fear responses, rather than erasing the fear memory itself.

Of course, a critically important question concerns how these and other inhibitory mechanisms are themselves silenced during fear relapse. That is, how does fear in response to an extinguished CS renew, for example, when the CS is presented outside the extinction context? One possibility is that the activity of inhibitory interneurons in the BA is context dependent; the activity of these neurons may be elevated in the extinction context but dampened in a dangerous context. Another possibility is that fear relapse is mediated by BA neurons that remain active after extinction. Clearly, further work is required to understand how target-specific silencing of BA neurons is modulated to allow for the context-dependent expression of fear. It is becoming clear that hippocampal and medial prefrontal cortical projections to basal and lateral amygdala neurons are involved in fear relapse after extinction (Herry et al., 2008; Knapska et al., 2012; Orsini et al., 2011). Whether these circuits ultimately suppress inhibitory activity in the amygdala or drive activity in BA neurons during fear relapse (or both) remains to be examined. Clearly, the use of activity-dependent neuronal tags to track neuronal populations engaged during encoding and retrieval processes is a promising strategy to answer these questions.

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Inhibition Mediates Top-Down Control of Sensory Processing

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In this issue of *Neuron*, Hamilton et al. (2013) stimulate identified inhibitory interneurons with optogenetics, revealing powerful control of the flow of sensory responses across cortical layers. During natural behavior, these influences may mediate the rapid adaptive abilities necessary for detection and perception of sensory signals in noisy environments.

There have been numerous reports over the years, recently at an accelerating pace, of rapid, behaviorally driven modulation of neuronal responses, receptive fields, and the underlying neuronal circuitry reflecting task reward, goals, and ongoing challenges faced during task performance (Ding and Simon, 2012; Fritz et al., 2003; Mesgarani and Chang, 2012).

There is increasing evidence that many of these modulatory effects are mediated by top-down signals originating in the prefrontal cortex (PFC) and are induced by cognitive functions such as attention, expectations, and reward. These influences are ultimately manifested as modulation of activity in primary sensory cortices that is mediated by specific cell populations that control the responsiveness of cortical outputs.

In this issue of *Neuron*, Hamilton et al. (2013) report on the influential role of a population of Parvalbumin-positive (PV) inhibitory neurons in modifying sensory responses in mouse auditory cortex. Hamilton et al. (2013) marshal a range of new experimental and computational approaches to explore how activation of the PV neurons effectively and rapidly changes the efficacy of auditory processing. Their experiments reveal many exciting and unexpected findings, yielding a key insight that most of the measured effects of PV activation are the result of relatively straightforward modulation of the gain of bottom-up flow in the feedforward circuits enhancing activity across all cortical layers, rather than of the more complex lateral interactions within the same layers.

To arrive at these conclusions, Hamilton et al. (2013) effectively and seamlessly combined three powerful experimental approaches. The first is the optogenetic stimulation of PV inhibitory cells that have been transfected with the light-sensitive ion channel ChR2. This allowed them to observe the effects of selective activation of this important cell population, which makes up more than half of the inhibitory neurons in the cortex and which has been shown to play an important role in synchronizing cortical activity and networks (Cardin et al., 2009). These PV neurons are also the likely recipients of top-down influences from higher cortical regions via the substantial inhibitory inputs from vasoactive intestinal polypeptide (VIP)-expressing neurons that in turn are susceptible to rapid cholinergic and serotonergic neuromodulation (Arroyo et al., 2012).

The second technical approach concerns the use of multielectrode arrays that facilitated simultaneous recordings from many sites spread out laterally and in-depth along and across cortical layers. Simultaneous recordings are essential to determine the strength, directionality, and sign of neuronal interactions. These in turn reveal the "effective" functional connectivity among neurons under different stimulation modes (or behavioral states under natural conditions).

Third, to determine the modulations in neuronal connectivity and sensitivity, Hamilton et al. (2013) imaginatively and efficiently exploited two computational analyses. One is based on *Ising* models in which an assessment of the connectivity among sites is determined by optimally accounting for all correlations simultaneously (or the so-called fully connected model). Hamilton et al. (2013) first validate this approach as a viable method of analysis using the known effects of tonal stimulation and of the (vertical and horizontal) organization of cortical layers in the normal state of the animal. Then, under optical stimulation (and PV activation), the same analysis revealed a very different and surprising picture: the vertical (across layer—and within column) connectivity was significantly enhanced, while the horizontal (within layer) interactions remained unchanged. This pattern effectively strengthened the coupling of the feedforward thalamocortical input to other cortical layers within a column.

The *Ising* models are agnostic to the directionality of the correlations among neuronal sites. For this, it is necessary to appeal to linear regression analyses that incorporate a time history of the responses to render an estimate of the spectrotemporal receptive fields (STRFs) of a given site relative to all other sites. These estimates confirmed that upon optical stimulation of PV cells, superficial layers were indeed more affected by inputs from layer 4, with little within-layer changes.

Finally, another fascinating result of PV stimulation is the strong depression of spontaneous activity but relatively weaker reduction of stimulus responses, coupled with a narrowing of A1 tuning curves. These changes effectively enhance the signal-to-noise ratio, significantly improving the detection of a signal (tone) against the "quieter" spontaneous background, thus explaining how previous optogenetic activation of PV neurons enhanced stimulus feature selectivity in cortical neurons (Atallah et al., 2012).

The importance of the Hamilton et al. (2013) findings can be best appreciated when viewed in the context of previous studies. For instance, the effects of PV stimulation are remarkably consistent with those induced during behavioral task performance by attention and expectations on sensory cortical responses, including the suppressive effects of sensory responses (Otazu et al., 2009) and the hypotheses implicating inhibitory interneurons in mediating attention effects (Mitchell et al., 2007). The suppressive effects are also seen during short-term memory and expectation (Jaramillo and Zador, 2011; Linke et al., 2011; Wiggs and Martin, 1998).

PV inhibitory neurons are ubiquitous in the brain. Recent recordings of optogenetically tagged PV cell responses in mouse prefrontal cortex during natural foraging behavior have revealed a strong correlation between their responses and specific behavioral events "leaving a reward zone" (Pi et al., 2013). This suggested a role for these cells in controlling the flow of information (especially pyramidal cell outputs) during behavioral events. In another series of experiments, the effects of inhibiting PV cells in the auditory cortex by optogenetic stimulation of the VIP neurons resulted in effectively disinhibiting auditory cortical responses and hence increasing the gain of cortical responses (Kvitsiani et al., 2013). This is consistent with the effects of stimulating PV cells in Hamilton et al. (2013)'s work, and with the effects of electrically stimulating the PFC on auditory cortical receptive fields and responses (Winkowski et al., 2013). Thus, all these findings provide complementary views of the stages mediating PFC regulation and learning of information in sensory cortices.

While these exciting studies hint at the functionality of the different cell populations in the cortex during behavior, and emphasize the importance of PV neurons in enhancing feedforward connectivity, they still leave unanswered the fundamental question of mechanism—how do these adaptive effects take place so rapidly during behavior? Are these dynamic adjustments in effective functional assemblies formed by presynaptic gating of incoming information flow, by adjusting postsynaptic response

strength, or by shaping of pyramidal cell output by inhibitory interneurons, or by a combination of these processes at different times during behavior? The answers to these questions will undoubtedly require further technical enhancements that enable observation and controlled perturbation of neural activity in various targeted cell populations during behavioral states with precisely defined task demands. With the introduction of new optogenetic targeting and labeling techniques, exploration of the neural bases of behavior is about to enter a new and exciting phase.

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